REMARKS

At the outset, Applicants thank the Examiners for the courtesy of an interview of August 18, 2003. In accordance with the discussion during the telephone interview and suggestions by the Examiners to address their concerns, the following remarks and the attached unexecuted Declaration are provided (the executed Declaration will follow as soon as possible). Claims 16-17 and 21-28 are pending in this application. Claims 16-17 and 21-28 have been rejected. No new matter has been added by this amendment. Reconsideration is respectfully requested.

I. Rejection of Claims 16 and 17 under 35 U.S.C. §103

Claims 16 and 17 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ross et al. (hereinafter Ross) in view of Niman et al. (hereinafter Niman).

The Examiner suggests that Ross teach that a polyclonal antibody capable of binding to BCRP protein can be prepared by immunizing a mammal with a preparation of BCRP or a functional derivative of BCRP which encompass fragments containing the extracellular epitope, the antibodies produced by this method are

suggested to inherently comprise antibodies that recognize the extracellular portion of a BCRP. The Examiner suggests that with respect to the natural conformation of a protein, a purified protein may or may not change its natural conformation. It is suggested that neither the prior art nor the specification teach the BCRP changes its natural conformation when purified.

The Examiner further suggests that Ross teach that a monoclonal antibody could be prepared by the method taught [in reference 7] in the Ross patent. It is suggested that cell fusion between myeloma cells and antibody producing cells resulted in antibodies recognizing SRBC.

The specification is suggested to fail to teach any new method that is different from the teachings of the prior art.

Further, the claims are suggested to only require that the antibody recognizes an extracellular portion of a BCRP. It is suggested that even if the antibodies were prepared from a purified protein that had changed its natural conformation, the antibodies would still comprise those that recognize the extracellular epitope of the BCRP.

Further, it is suggested that Niman teach the method of making monoclonal antibodies against immunogenic polypeptides and

oncoprotein ligand, and thus the antibody has to recognize the extracellular portion of a protein. The Examiner suggests that it would have been obvious to one of skill to employ the methods taught by Ross and Niman to make an antibody to BCRP with a reasonable expectation of success. Applicants respectfully disagree.

First, Applicants' invention is an isolated antibody that recognizes an extracellular portion of a BCRP in its natural conformation, see specification at page 9, lines 21-22; and see claims 16-17 and 21-28. This antibody is unique and distinct in that at the time of filing of this application there was no method known in the art to produce an isolated antibody that recognized an extracellular portion of an ABC transporter (such as BCRP) in a living cell.

Further, one of skill would not have expected that a reliable method could be achieved for generating antibodies which could specifically recognize the extracellular portion of BCRP due to the very small extracellular domain which would be available as a target to such an antibody. Because of the small target domain, one of skill would not have expected to be successful in effectively or consistently isolating such

antibodies from a generic preparation of antibodies made against purified BCRP protein.

To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a) three basic criteria must be met. MPEP § 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations.

The cited references fail to meet all of these criteria with respect to the instant, claimed invention. Contrary to the Examiner's suggestion, one of skill would not have had any reasonable expectation of successfully identifying an antibody to a small domain target, such as the extracellular epitope of BCRP in its natural conformation, using the prior art methods taught by Ross (U.S. Patent 6,313,277) and Niman (U.S. Patent 5,563,247).

Ross teaches the preparation of antibodies using a purified protein at column 4, lines 50-57. However, there is no teaching in Ross for generating antibodies which will specifically

recognize the extracellular portion of BCRP. Further, there is no teaching or suggestion of successfully isolating such antibodies from a generic preparation of antibodies made against purified BCRP protein.

A person skilled in the art would not expect to be able to generate an antibody that recognizes the extracellular portion of BCRP, using the approach suggested by the Examiner. The antibody generation technique proposed by the Examiner is not predictable, and would provide no reasonable expectation of success, as also corroborated in the attached Declaration at paragraph 3. This is especially true when applied to ABC transporter proteins like BCRP, because the extracellular domain of these proteins is small relative to the size of the entire protein, which results in a difficult target for the antibodies, as also corroborated in the attached Declaration at paragraphs 4 through 6 .

Further, a purified protein is different than the natural conformation required by the claims of the present invention, see specification at page 9, lines 20-23; and as also corroborated in the attached Declaration at paragraph 5. In this particular ABC transporter class of proteins, the proteins are inserted in the plasma membrane. As noted in the accompanying expert

declaration, BCRP forms a homodimer in the cell membrane. This conformation would be expected to be very different from the conformation adopted by purified, monomeric BCRP protein or protein fragment. As a result, any antibody generated according to Ross against a purified BCRP protein or fragment thereof would not be expected to recognize the extracellular domain of BCRP in its natural conformation.

Similarly, the Niman method would not be predictable when applied to ABC transporter proteins, such as BCRP. Niman teaches making an antibody to a surface protein by using a whole cell technique which one of skill would not believe to be effective for use with ABC transporters. As noted by the expert declarant at paragraph 6, the general technique of using whole cells as immunogens to generate antibodies to extracellular epitopes of cell membrane proteins does not work well for ABC transporters, and would not be expected to work for BCRP. ABC transporters (such as BCRP) have only a few small domain areas which are available as targets for use with antibodies, as also corroborated in the attached Declaration at paragraph 6.

The advantages of the present invention include the availability of the screening assay which is free from competing

background products and which efficiently achieves high expression of the antibodies. Accordingly, the combination of Ross and Niman fail to provide the information necessary to teach or suggest all of the claim limitations of the present invention. See also the attached Declaration at paragraphs 4-6.

The actual antibody preparation set forth in the specification highlights the advantages of the present invention relative to existing techniques, and the requirements for antibody recognition. For instance, as demonstrated on page 39 of the specification, a human BCRP cDNA (obtained as a full length EST) was cloned into a Harvey murine sarcoma virus backbone to create the HaBCRP retroviral vector. This vector was next introduced into the ecotropic packaging cell line GPE86 and vector-containing supernatant was used to transduce NIH 3T3 cells. A polyclonal population of cells (designated 3T3-BCRP) was isolated by flow cytometry, gating on cells that efflux the fluorescent dye Hoechst 33342. Expression of the HuBCRP gene product in these cells was confirmed by Western blot analysis, see specification at page 39, lines 4-10.

The 3T3-BCRP cells were used to immunize mice, see specification at page 39, line 11. Individual mice that showed antibody reactivity in the serum were killed and hybridoma clones were isolated after cell fusion and selection. Supernatants from each hybridoma clone were screened by flow cytometry using a human breast cancer cell line (MCF-7) that had been transduced with an amphotrophic HaBCRP vector, see specification at page 39, lines 15-19. Any supernatant that showed reactivity in this assay was then back-screened on the parental MCF-7 line and clones that reacted with the MCF-7 HaBCRP cells but not with the parental MCF-7 line were scored as positive and specific. These cells were subcloned and re-screened based on the indicator cell lines, see Figure 1, and specification at page 39, lines 19-24. Independent subclones that showed relatively large shifts with the MCF-7 HaBCRP cells, but not with the parental control cells were then isolated. Clones that detected expression of the HaBCRP vector in bone marrow cells from previously transplanted mice were expanded to produce larger quantities of supernatant *ex vivo* with a rollerbottle production system, see specification at page 39, lines 25-29. The antibodies were then purified on an

affinity column. These antibodies were then tested for their ability to detect the endogenously expressed huBCRP gene product in human umbilical cord blood samples. Efficient and high expression of the antibodies was achieved.

Applicants believe that the preceding remarks fully address the Office action and the Examiner's issues. Neither Ross nor Niman alone or combined teach the effective generation of isolated antibodies to ABC transporters in a natural conformation. Neither Ross nor Niman provide any reasonable expectation of success in achieving the present invention.

Withdrawal of this rejection is respectfully requested.

II. Rejection of Claims 16, 17 and 21-28 under 35 U.S.C. §103

Further claims 16 and 17 and 21-28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ross in view of Niman as applied to claims 16, 17, 21, 22, 25, and 26 and further in view of Godfrey et al. (U.S. 6,528,623).

The Examiner suggests that claims 23, 24, 27, and 28 are drawn to an isolated BCRP which is preferably humanized.

The Examiner acknowledges that the combined teachings of Ross and Niman do not disclose a chimeric or humanized antibody.

Godfrey et al. is suggested to teach an antibody to a receptor on the surface of activated CD4+ T cells, preferably the antibody is humanized. Godfrey is further suggested to teach that humanized antibodies are less likely to cause immunological response when used in human therapy. Godfrey is also suggested to teach methods of producing such chimeric humanized antibodies (columns 19-22). The Examiner suggests that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the methods taught by Ross and Niman with that of Godfrey to make an antibody to BCRP with a reasonable expectation of success. Applicants respectfully disagree.

As set forth fully above, Ross and Niman, individually or combined, fail to teach or suggest the present invention. Godfrey does not provide any further teaching or suggestion which would motivate one of skill to arrive at the instant invention.

Godfrey teaches fragments and ligand fragments to a receptor on the surface of activated CD4+T cells. The fragments are purified extracellular domains of ligands (see abstract. Column 3, line 4). Humanized antibodies are also taught to the purified

fragments. Godfrey does not teach or suggest an isolated antibody to a small domain target, such as the extracellular epitope of BCRP in its natural conformation.

As set forth above, the present invention generates an antibody targeted to a very small domain, namely the extracellular epitope of BCRP in its live or natural conformation. The antibody of the present invention is produced by introducing an immunogen into a retroviral vector. The retroviral vector allows production of a screening assay which is background free and also achieves high antibody expression. The key to driving the production of this antibody is the ratio of correct clones relative to the background. Elimination of the competing background products allows antibodies for small domain targets to be identified. The present invention effectively reduces the signal to noise ratio.

At the time of filing of this application there was no method known in the art to produce an isolated antibody that recognized an extracellular portion of a ABC transporter (such as BCRP) in a living cell. One of skill would not have expected that a reliable method could be achieved for generating such

antibodies which could specifically recognize the extracellular portion of BCRP.

Applicants submit that the Examiner has not met the burden of proof required under MPEP 706.02. The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

There is no suggestion in any of the recited prior art referenced that it would have been even plausible to isolate antibodies from a generic preparation of antibodies made against purified BCRP protein. Further, it is not taught or suggested that antibodies to a purified denatured protein could recognize the extracellular epitope of an ABC transporter in its live or natural conformation as required by the present claims.

Thus, the combination of prior art suggested by the Examiner does not provide any teaching or suggestion to produce the invention claimed in claims 16, 17 and 21-28. Further, based upon the teachings of Ross, Niman and Godfrey, one of skill would not have any reasonable expectation of successfully generating an isolated antibody which recognizes an extracellular portion of a BCRP in its natural conformation.

Withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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